Citation:

de Munter JSL, Hu FB, Spiegelman D, Franz M, van Dam RM. Whole grain, bran and germ intake and risk of type 2 diabetes: A prospective cohort study and systematic review. *PLoS Med* 2007; 4 (8): e261.

PubMed ID: 17760498

Study Design:

Prospective cohort study; Meta-analysis

Class:

M - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To systematically evaluate the strength of the epidemiological evidence for a relation between intakes of whole grain, bran and germ and risk of type 2 diabetes (T2D) in prospective cohort studies.

Inclusion Criteria:

Cohort Study

Women in the United States from the Nurses' Health Studies I and II.

Systematic Review

- Prospective cohort studies
- T2D as end-point
- Description of the whole grain assessment
- Presentation of relative risks (RR) with a measure of variability
- Description of adjustment for potential confounders.

Exclusion Criteria:

Cohort Study

- Participants who did not complete the baseline food-frequency questionnaire (FFQ)
- Participants who left 12 or more (from Nurses' Health Study I) or 10 or more (Nurses' Health Study II) items blank
- Participants who had implausible reported total energy intakes (<600kcal per day or >3,500kcal per day)
- No history of diabetes (including gestational diabetes), cardiovascular disease (CVD) or

cancer at baseline.

Systematic Review

- Review papers
- Comments and editorials
- Diabetes not studied as end-point
- Cross-Sectional studies
- Other dietary factors studied.

Description of Study Protocol:

Recruitment

- Cohort Study
  - Women in the United States from the Nurses' Health Studies I (began in 1976: 121,700 female registered nurses returned a mailed questionnaire) and II (began in 1989: 116,609 female registered nurses returned a mailed questionnaire)
  - Baseline year chosen based on use of FFQ.
- Systematic Review
  - Other prospective cohort studies were identified in searches of MEDLINE and EMBASE up to January 2007, using keywords of "diabetes mellitus, type 2", "whole grain*", "dietary fiber", "cereals."

Design

Prospective cohort study; Meta-analysis and Systematic review.

Blinding Used

Not applicable.

Intervention

- Cohort study: Dietary intakes and potential confounders were assessed with regularly administered questionnaires (every two years)
- Systematic review: Data were independently extracted by two reviewers.

Statistical Analysis

- Cohort Study
  - Cox proportional hazards analysis used to estimate the relative risk for T2D according to dietary intakes
  - Person-years of follow-up were counted from the date of return from the baseline questionnaire until the date of diabetes diagnosis, death or the end of follow-up, whichever came first
  - Dietary variables were categorized in quintiles of intake and non-dietary covariates were updated by using the most recently assessed exposure for each two-year follow-up period
  - To test for linear trends across quintiles of intake, the quintile medians were modeled as a continuous variable
  - Pearson correlations were calculated between dietary intakes with adjustment for total energy intake

- Proportion of association between whole grain intake and risk of T2D explained by BMI and the corresponding 95% CI was estimated based on the change in regression coefficients after adding BMI to the multivariate model (as described by Lin et al).
- Systematic Review
  - Summary measures were calculated from the logarithm of the relative risks and corresponding standard errors of the individual studies using random effects models that incorporate both a within-study and an additive between-studies component of variance
  - P-values for heterogeneity of study results were calculated using Cochran Q test
  - Meta-regression of log (RR) of the studies as the dependent variable on the log (median) whole grain intake of the study population
  - Begg and Egger test and visual inspection of the funnel plot were used to evaluate possible publication bias.

Data Collection Summary:

Timing of Measurements

- Data on whole grain intake and risk of T2D after 18 years of follow-up
- Questionnaires administered every two years.

Dependent Variables

- Cases of T2D were identified from the mailed questionnaire
- Women who reported diabetes were mailed an additional questionnaire and cases were diagnosed according to criteria of the National Diabetes Data Group and the American Diabetes Association. Validation study showed 98% confirmation of self-reported T2D after review of medical record.

Independent Variables

- Dietary intake of whole grain, bran and germ assessed with regularly administered semiquantitative food-frequency questionnaires (FFQ) asking about average food intake during the past year, with responses given in commonly used portion sizes
- Portions converted to gram weights per serving and intakes of nutrients computed and whole grain food composition database developed. Pearson correlation coefficient for estimates derived from FFQs and diet records corrected for within-person variation ranged from 0.58 and 0.79.

Control Variables

- Age
- Height, weight, BMI
- Smoking status
- Use of post-menopausal hormone therapy
- Use of oral contraceptives (for Nurses Health Study II)
- Personal history of diabetes, CVD and cancer
- Physical activity.

Description of Actual Data Sample:

- *Initial N:*
  - Cohort study: 121,700 nurses in Nurses' Health Study I, 116,609 nurses in Nurses' Health Study II
  - Systematic review: 45 articles identified and two current studies
- *Attrition (final N):*
  - Cohort study: 73,327 nurses in Nurses' Health Study I and 88.410 in Nurses' Health Study II remained after exclusions applied
  - Systematic review*:* Six studies included (five cohort studies and current study)
- *Age at baseline:*
  - 37-65 years for Nurses' Health Study I
  - 26-46 years for Nurses' Health Study II
- *Ethnicity:*
  - Cohort study: Not reported
  - Systematic review: Cohorts included predominantly white or black populations
- *Other relevant demographics:* None mentioned
- *Anthropometrics:* None mentioned
- *Location:*
  - Cohort study: United States
  - Systematic review*:* United States and Finland.

Summary of Results:

Relative Risks (95% CI) of Type 2 Diabetes According to Whole Grain Intake

Study/Statistic NHS I: 1984-2002 NHS II: 1991-2003	Q1 (Low)	Q2	Q3	Q4	Q5 (High)	P-Value, Test for Trend
NHS I: Median (g per day)	3.7	8.4	13.2	19.5	31.2	--
NHS I: Number of cases	1,036	1,064	984	905	758	--
NHS I: Person-years	246,470	248,117	246,964	246,920	246,932	--
NHS I: Age-adjusted RR	1 (ref)	0.92 (0.84-1.00)	0.80 (0.73-0.87)	0.70 (0.63-0.76)	0.56 (0.51-0.62)	<0.001
NHS I: Multivariate RR	1 (ref)	0.94 (0.86-1.02)	0.83 (0.76-0.91)	0.73 (0.66-0.80)	0.63 (0.57-0.69)	<0.001
NHS I: BMI	1 (ref)	0.92 (0.84-1.00)	0.84 (0.77-0.92)	0.79 (0.72-0.87)	0.75 (0.68-0.83)	<0.001

NHS II: Median (g per day)	6.2	12.6	18.6	26.1	39.9	--
NHS II: Number of cases	436	395	359	297	252	--
NHS II: Person-years	208,575	208,692	207,539	207,794	207,536	--
NHS II: Age-adjusted RR	1 (ref)	0.84 (0.73-0.96)	0.73 (0.63-0.84)	0.58 (0.50-0.68)	0.49 (0.42-0.57)	<0.001
NHS II: Multivariate RR	1 (ref)	0.93 (0.81-1.07)	0.86 (0.75-1.00)	0.74 (0.63-0.86)	0.68 (0.57-0.81)	<0.001
NHS II: BMI	1 (ref)	0.94 (0.82-1.08	0.90 (0.78-1.05)	0.81 (0.69-0.95)	0.86 (0.72-1.02	0.03

Other Findings

Cohort Study

- 6,486 cases of T2D were documented during 12-18 years of follow-up; 4,747 cases during 1,235,403 person-years of follow-up in the Nurses' Health Study I and 1,739 cases during 1,040,136 person-years in the Nurses' Health Study II
- Higher intakes of whole grain were associated with a higher physical activity, lower BMI, lower likelihood of smoking, and a lower consumption of alcohol, soft drinks and processed meats
- The median whole grain intake in the lowest and highest quintile was 3.7 and 31.2g per day for Nurses' Health Study I and 6.2 and 39.9g per day for Nurses' Health Study II
- After adjustment for potential confounders, the RR for the highest compared to the lowest quintile of whole grain intake was 0.63 (95% CI: 0.57-0.69) for Nurses' Health Study I and 0.68 (95% CI: 0.57-0.81) for Nurses' Health Study II (both P<0.001 for trend)
- After further adjustment for BMI, RR for the highest compared to the lowest quintile of whole grain intake was 0.75 (95% CI: 0.68-0.83, P<0.001 for trend) for Nurses' Health Study I and 0.86 (95% CI: 0.72-1.02, P<0.03 for trend) for Nurses' Health Study II
- In the multivariate analysis, after adjustment for BMI, each 40g increment in whole grain intake was associated with a RR of diabetes of 0.70 (95% CI: 0.62-0.79) for Nurses' Health Study I and 0.83 (95% CI: 0.70-0.98) for Nurses' Health Study II
- Associations for bran intake were similar to those for total whole grain intake (RR 0.70, 95% CI: 0.62-0.79 for extreme quintiles, P<0.001 for trend), whereas there was no significant association observed for germ intake after adjustment for bran.

Systematic Review

- Based on pooled data for six cohort studies including 286,125 participants and 10,944 cases of T2D, a two-serving per day increment in whole grain consumption was associated with a pooled RR of T2D of 0.79 (95% CI: 0.72-0.87) after adjustment for potential confounders and BMI

- Visual inspection of the funnel plot and Begg and Egger tests did not suggest publication bias.

Author Conclusion:

- Findings from prospective cohort studies consistently indicate that higher consumption of whole grains can contribute to the prevention of T2D
- Cross-sectional studies and short-term randomized trials have provided additional evidence for beneficial effects of whole grains on glucose homeostasis
- Evidence for beneficial metabolic effects is stronger for consuming a variety of whole grains than for wheat bran in isolation
- These data provide further support for recommendations to increase consumption of whole grains including whole wheat, whole oats, oatmeal, whole grain corn and popcorn, brown and wild rice, whole rye, whole grain barley, buckwheat, triticale, bulgur, millet, quinoa and sorghum
- Based on a meta-analysis of six cohort studies, a two-servings-per-day increment in whole grain intake was associated with a 21% decrease in risk of T2D.

Reviewer Comments:

Authors note the following strengths and limitations:

- *Prospective design and high rates of follow-up minimize probability of recall bias or selection bias*
- *Residual confounding by additional unmeasured or imperfectly measured confounders cannot be excluded, but consistency in findings across different cohorts reduces that likelihood*
- *Measurement error in the assessment of dietary intakes is inevitable*
- *Diabetes assessed by self-report confirmed by supplementary questionnaire since screening for blood glucose was not feasible given cohort size; however, study population consisted of nurses with access to medical care.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes

4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes

4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A

7.	**Were outcomes clearly defined and the measurements valid and reliable?**		Yes
	7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
	7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
	7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
	7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	???
	7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
	7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
	7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
	8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes